SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bicalutamide tablets 50mg BYPRO

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains:
Bicalutamide 50 mg
Colour: Titanium Dioxide Ph.Eur.

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BYPRO (Bicalutamide tablet) 50 mg daily is indicated for use in combination therapy with a luteinizing hormone releasing hormone (LHRH) analogue for the treatment of Stage D_2 metastatic carcinoma of the prostate.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The recommended dose for bicalutamide therapy in combination with an LHRH analogue is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that bicalutamide be taken at the same time each day. Treatment with bicalutamide should be started at the same time as treatment with an LHRH analogue.

Dosage Adjustment in Renal Impairment
No dosage adjustment is necessary for patients with renal impairment.

Dosage Adjustment in Hepatic Impairment
No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. In patients with severe liver impairment (n=4), although there was a 76% increase in the half-life (5.9 and 10.4 days for normal and impaired patients, respectively) of the active enantiomer of bicalutamide no dosage adjustment is necessary.

4.3 CONTRAINDICATIONS

Hypersensitivity
BYPRO (Bicalutamide tablet) is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components. Hypersensitivity reactions including angioneurotic edema and urticaria have been reported.

Women

BYPRO (Bicalutamide tablet) has no indication for women, and should not be used in this population.

Pregnancy

BYPRO (Bicalutamide tablet) may cause fetal harm when administered to a pregnant woman. BYPRO (Bicalutamide tablet) is contraindicated in women, including those who are or may become pregnant. There are no studies in pregnant women using Bicalutamide. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the fetus.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatitis

Rare cases of death or hospitalization due to severe liver injury have been reported postmarketing in association with the use of bicalutamide. Hepatotoxicity in these reports generally occurred within the first three to four months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of bicalutamide patients in controlled clinical trials.

Serum transaminase levels should be measured prior to starting treatment with bicalutamide, at regular intervals for the first four months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, “flu-like” symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or their ALT rises above two times the upper limit of normal, bicalutamide should be immediately discontinued with close follow-up of liver function.

Glucose Tolerance

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycemic control in those with preexisting diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving Bicalutamide in combination with LHRH agonists.

Laboratory Tests

Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient’s response. If PSA levels rise during Bicalutamide therapy, the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment-free period of antiandrogen, while continuing the LHRH analog, may be considered.

Pediatric Use

The safety and effectiveness of bicalutamide in pediatric patients have not been established.

bicalutamide orodispersible tablet was studied in combination with anastrozole orodispersible tablet in an open-label, non-comparative, multi-center study that assessed the efficacy and safety of this combination regimen over 12 months in the treatment of gonadotropin-independent precocious puberty in boys with familial male-limited precocious puberty, also known as testotoxicosis. Patients were enrolled in the study if they had a baseline age ≥ 2 years and a diagnosis of testotoxicosis based on clinical features of progressive precocious puberty, symmetrical testicular enlargement, advanced bone age, pubertal levels of serum testosterone, prepubertal pattern of gonadotropin secretion following a GnRH stimulation test, and absence of other clinical and biochemical causes of testosterone excess. Thirteen out of the 14 patients enrolled completed 12 months of combination treatment (one patient was lost to follow-up). If central precocious puberty (CPP) developed an LHRH analog was to be added. Four patients were diagnosed with CPP during the 12-month study and received LHRH analog treatment and 2 additional patients were diagnosed at the end of the 12 months and received treatment subsequently. Mean ± SD characteristics at baseline were as follows: chronological age: 3.9±1.9 years; bone age 8.8±2.5; bone age/chronological age ratio: 2.06 ± 0.51; growth rate (cm/yr): 10.81 ± 4.22; growth rate standard deviation score (SDS): 0.41 ± 1.36.

The starting bicalutamide dose was 12.5 mg. Bicalutamide was titrated in each patient until steady-state Rbicalutamide (the active isomer of bicalutamide) trough plasma concentration reached 5-15 mcg/mL, which is the range of therapeutic concentrations achieved in adults with prostate cancer following the administration of the currently approved bicalutamide dose of 50 mg. The starting daily dose of anastrozole was 0.5 mg. Anastrozole was independently titrated in each patient until it reached at steady-state a serum estradiol concentration of <10 pmol/L (2.7 pg/mL). The following ascending doses were used for bicalutamide: 12.5 mg, 25 mg, 50 mg, and 100 mg. For anastrozole there were two ascending doses: 0.5 mg and 1 mg. At the end of the titration phase 1 patient was on 12.5 mg bicalutamide, 8 patients were on 50 mg bicalutamide, and 4 patients were on 100 mg bicalutamide; 10 patients were on 0.5 mg anastrozole and 3 patients were on 1 mg anastrozole. In the majority of patients, steady-state trough concentrations of R-bicalutamide appeared to be attained by Day 21 with once daily dosing. Steady-state trough plasma anastrozole concentrations appeared to be attained by Day 8.

The primary efficacy analysis of the study was to assess the change in growth rate after 12 months of treatment, relative to the growth rate during the ≥6 months prior to entering the study. Pre-study growth rates were obtained retrospectively. There was no statistical evidence that the growth rate was reduced during treatment. During bicalutamide/ anastrozole treatment the mean growth rate (cm/yr) decreased by 1.6 cm/year, 95% CI (-4.7 to 1.5) p=0.28; the mean growth rate SDS decreased by 0.1 SD, 95% CI (–1.2 to 1.0) p=0.88. Table 2 shows descriptive data for growth rates for the overall population and for subgroups defined by history of previous treatment for testotoxicosis with ketoconazole, spironolactone, anastrozole or other aromatase inhibitors.

Table 1. Growth rates

Endpoint	Analysis population	Pre-study Mean	Change from pre-study to 12 months			% patients with growth reduction [1]
			Mean	Median	(Min, Max)	
Growth rate (cm/yr)	All treated (n=13)	10.8	-1.6	-2.8	(-7.4, 8.4)	9/13 (69%)
	PT [2] (n=6)	10.3	-0.2	-2.6 [4]	(-7.2, 8.4)	4/6 (67%)
	NPT[3] (n=7)	11.2	-2.8	-2.8	(-7.4, 1.1)	5/7 (71%)
Growth rate(SD units)	All treated (n=13)	0.4	-0.1	-0.4	(-2.7, 3.5)	9/13 (69%)
	PT 2 (n=6)	-0.1	+0.7	-0.2 4	(-1.6, 3.5)	4/6 (67%)
	NPT3 (n=7)	0.8	-0.7	-0.4	(-2.7, 0.5)	5/7 (71%)

[1] Change compared to pre-study growth rate

[2] PT = Previous treatment for testotoxicosis with ketoconazole, spironolactone, anastrazole or other aromatase inhibitors

[3] NPT = no previous treatment for testotoxicosis with ketoconazole, spironolactone, anastrozole or other aromatase inhibitors

[4] Median calculated as midpoint of 3rd and 4th ranked observations

Total testosterone concentrations increased by a mean of 5 mmol/L over the 12 months of treatment from a baseline mean of 10 mmol/L. Estradiol concentrations were at or below the level of quantification (9.81 pmol/L) for 11 of 12 patients after 12 months of treatment. Six of the 12 patients started treatment at an estradiol concentration below the level of quantification.

There were no deaths, serious adverse events, or discontinuations due to adverse events during the study. Of the 14 patients exposed to study treatment, 13 (92.9%) experienced at least one adverse event. The most frequently reported (>3 patients) adverse events were gynecomastia (7/14, 50%), central precocious puberty (6/14, 43%), vomiting (5/14, 36%), headache (3/14,

21%), pyrexia (3/14, 21%) and upper respiratory tract infection (3/14, 21%). Adverse reactions considered possibly related to bicalutamide by investigators included gynecomastia (6/14, 43%), central precocious puberty (2/14, 14%), breast tenderness (2/14, 14%), breast pain (1/14, 7%), asthenia (1/14, 7%), increased alanine aminotransferase [ALT] (1/14, 7%), increased aspartate aminotransferase [AST] (1/14, 7%), and musculoskeletal chest pain (1/14, 7%). Headache was the only adverse reaction considered possibly related to anastrazole by investigators. For the patient who developed elevated ALT and AST, the elevation was <3X ULN, and returned to normal without stopping treatment; there was no concomitant elevation in total bilirubin.

Geriatric Use
In two studies in patients given 50 or 150 mg daily, no significant relationship between age and steady-state levels of total bicalutamide or the active R-enantiomer has been shown.

Hepatic Impairment
Bicalutamide should be used with caution in patients with moderate-to-severe hepatic impairment. Bicalutamide is extensively metabolized by the liver. Limited data in subjects with severe hepatic impairment suggest that excretion of bicalutamide may be delayed and could lead to further accumulation. Periodic liver function tests should be considered for hepatic-impaired patients on long-term therapy.

No clinically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. However, the half-life of the R-enantiomer was increased approximately 76% (5.9 and 10.4 days for normal and impaired patients, respectively) in patients with severe liver disease (n=4).

Renal Impairment
Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer.

Women
Bicalutamide has not been studied in women.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Clinical studies have not shown any drug interactions between bicalutamide and LHRH analogs (goserelin or leuprolide). There is no evidence that bicalutamide induces hepatic enzymes**.**

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4 with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity. Clinical studies have shown that with co-administration of Bicalutamide, mean midazolam (a CYP 3A4 substrate) levels may be increased 1.5 fold (for Cmax) and 1.9 fold (for AUC). Hence, caution should be exercised when Bicalutamide is co-administered with CYP 3A4 substrates.

In vitro protein-binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients

already receiving coumarin anticoagulants who are started on Bicalutamide and adjustment of the anticoagulant dose may be necessary.

4.6 PREGNANCY AND LACTATION

Pregnancy
Pregnancy Category X: Based on its mechanism of action, Bicalutamide may cause fetal harm when administered to a pregnant woman. Bicalutamide is contraindicated in women, including those who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. While there are no human data on the use of Bicalutamide in pregnancy and Bicalutamide is not for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus.

In animal reproduction studies, male offspring of rats receiving doses of 10 mg/kg/day (approximately 2/3 of clinical exposure at the recommended dose) and above, were observed to have reduced anogenital distance and hypospadias. These pharmacological effects have been observed with other antiandrogens. No other teratogenic effects were observed in rabbits receiving doses up to 200 mg/kg/day (approximately 1/3 of clinical exposure at the recommended dose) or rats receiving doses up to 250 mg/kg/day (approximately 2 times the clinical exposure at the recommended dose).

Nursing Mothers
Bicalutamide is not indicated for use in women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Bicalutamide is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally somnolence may occur. Any affected patients should exercise caution.

4.8 UNDESIRABLE EFFECTS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience
In patients with advanced prostate cancer treated with Bicalutamide in combination with an LHRH analog, the most frequent adverse reaction was hot flashes (53%).

In the multicenter, double-blind, controlled clinical trial comparing Bicalutamide 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analog, the following adverse reactions with an incidence of 5% or greater, regardless of causality, have been reported.

Table 2 Incidence of Adverse Events (≥ 5% in Either Treatment Group) Regardless of Causality

Body System Adverse Event	**Treatment Group Number of patients (%)**	
	Bicalutamide Plus LHRH Analogue (n=401)	**Flutamide Plus LHRH Analogue (n=407)**
Body as a Whole		
Pain (General)	142 (35)	127 (31)
Back Pain	102 (25)	105 (26)
Asthenia	89 (22)	87 (21)
Pelvic Pain	85 (21)	70 (17)
Infection	71 (18)	57 (14)
Abdominal Pain	46 (11)	46 (11)
Chest Pain	34 (8)	34 (8)
Headache	29 (7)	27 (7)
Flu Syndrome	28 (7)	30 (7)
Cardiovascular		
Hot Flashes	211 (53)	217 (53)
Hypertension	34 (8)	29 (7)
Digestive		
Constipation	87 (22)	69 (17)
Nausea	62 (15)	58 (14)
Diarrhea	49 (12)	107 (26)
Increased Liver Enzyme Test	30 (7)	46 (11)
Dyspepsia	30 (7)	23 (6)
Flatulence	26 (6)	22 (5)
Anorexia	25 (6)	29 (7)
Vomiting	24 (6)	32 (8)
Hemic and Lymphatic		
Anemia	45 (11)	53 (13)
Metabolic and Nutritional		
Peripheral Edema	53 (13)	42 (10)
Weight loss	30 (7)	39 (10)
Hyperglycemia	26 (6)	27 (7)
Alkaline Phosphatase Increased	22 (5)	24 (6)
Weight Gain	22 (5)	18 (4)
Muscoloskeletal		
Bone Pain	37 (9)	43 (11)
Myasthenia	27 (7)	19 (5)
Arthritis	21 (5)	29 (7)
Pathological Fracture	17 (4)	32 (8)
Nervous System		
Dizziness	41 (10)	35 (9)
Paresthesia	31 (8)	40 (10)
Insomnia	27 (7)	39 (10)
Anxiety	20 (5)	9 (2)
Depression	16 (4)	33 (8)

Respiratory System		
Dyspnea	51 (13)	32 (8)
Cough Increased	33 (8)	24 (6)
Pharyngitis	32 (8)	23 (6)
Bronchitis	24 (6)	22 (3)
Pneumonia	18 (4)	19 (5)
Rhinitis	15 (4)	22 (5)
Skin and Appendages		
Rash	35 (9)	30 (7)
Sweating	25 (6)	20 (5)
Urogenital		
Nocturia	49 (12)	55 (14)
Hematuria	48 (12)	26 (6)
Urinary Tract Infection	35 (9)	36 (9)
Gynecomastia	36 (9)	30 (7)
Impotence	27 (7)	35 (9)
Breast Pain	23 (6)	15 (4)
Urinary Frequency	23 (6)	29 (7)
Urinary Retention	20 (5)	14 (3)
Urinary Impaired	19 (5)	15 (4)
Urinary Incontinence	15 (4)	32 (8)

Other adverse experiences (greater than or equal to 2%, but less than 5%) reported in the bicalutamide-LHRH analogue treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality.

Body as a Whole
Neoplasm; Neck pain; Fever; Chills; Sepsis; Hernia; Cyst

Cardiovascular
Angina pectoris; Congestive heart failure; Myocardial infarct; Heart arrest; Coronary artery disorder; Syncope

Digestive
Melena; Rectal hemorrhage; Dry mouth; Dysphagia; Gastrointestinal disorder; Periodontal abscess; Gastrointestinal carcinoma

Metabolic and Nutritional
Edema; Bun increased; Creatinine increased; Dehydration; Gout; Hypercholesteremia

Musculoskeletal
Myalgia; Leg cramps

Nervous
Hypertonia; Confusion; Somnolence; Libido decreased; Neuropathy; Nervousness

Respiratory
Lung disorder; Asthma; Epistaxis; Sinusitis

Skin and Appendages
Dry skin; Alopecia; Pruritus; Herpes zoster; Skin carcinoma; Skin disorder

Special Senses
Cataract specified

Urogenital
Dysuria; Urinary urgency; Hydronephrosis; Urinary tract disorder

Abnormal Laboratory Test Values
Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, and creatinine and decreased hemoglobin and white cell count have been reported in both bicalutamide-LHRH analogue treated and flutamide-LHRH analogue treated patients.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of bicalutamide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Uncommon cases of hypersensitivity reactions, including angioneurotic edema and urticaria have been seen. Cases of interstitial lung disease (some fatal), including interstitial pneumonitis and pulmonary fibrosis, have been reported with bicalutamide. Interstitial lung disease has been reported most often at doses greater than 50 mg. A few cases of fatal hepatic failure have been reported.

Reduction in glucose tolerance, manifesting as diabetes or a loss of glycemic control in those with pre-existing diabetes, has been reported during treatment with LHRH agonists.

4.9 OVERDOSE

Long-term clinical trials have been conducted with dosages up to 200 mg of bicalutamide daily and these dosages have been well tolerated. A single dose of bicalutamide that results in symptoms of an overdose considered to be life threatening has not been established.

There is no specific antidote; treatment of an overdose should be symptomatic.

In the management of an overdose with bicalutamide, vomiting may be induced if the patient is alert. It should be remembered that, in this patient population, multiple drugs may have been taken. Dialysis is not likely to be helpful since bicalutamide is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Bicalutamide is a non-steroidal antiandrogen. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen.

When Bicalutamide is combined with luteinizing hormone-releasing hormone (LHRH) analogue therapy, the suppression of serum testosterone induced by the LHRH analogue is not affected. However, in clinical trials with bicalutamide as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted.

In a subset of patients who have been treated with Bicalutamide and an LHRH agonist, and who discontinue Bicalutamide therapy due to progressive advanced prostate cancer, a reduction in Prostate Specific Antigen (PSA) and/or clinical improvement (antiandrogen withdrawal phenomenon) may be observed.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Bicalutamide is well absorbed following oral administration, although the absolute bioavailability is unknown. Co-administration of bicalutamide with food has no clinically significant effect on rate or extent of absorption.

Distribution
Bicalutamide is highly protein-bound (96%).

Metabolism/Elimination
Bicalutamide undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.

Pharmacokinetics of the active enantiomer of Bicalutamide in normal males and patients with prostate cancer are presented in Table 3:

Parameter	**Mean**	**Standard Deviation**
Normal Males (n=30)		
Apparent Oral	0.320	0.103

Clearance (L/hr)		
Single Dose Peak Concentration (μg/mL)	0.768	0.178
Single Dose time to Peak Concentration (hours)	31.3	14.6
Half-life (days)	5.8	2.29
Patients with Prostate Cancer (n=40)		
Css (μg/mL)	8.939	3.504
Css= Mean Steady-State Concentration		

Clinical studies
Bicalutamide 50 mg Daily in Combination with an LHRH-A

In a multicenter, double-blind, controlled clinical trial, 813 patients with previously untreated advanced prostate cancer were randomized to receive Bicalutamide 50 mg once daily (404 patients) or flutamide 250 mg (409 patients) three times a day, each in combination with LHRH analogues (either goserelin acetate implant or leuprolide acetate depot).

In an analysis conducted after a median follow-up of 160 weeks was reached, 213 (52.7%) patients treated with bicalutamide-LHRH analogue therapy and 235 (57.5%) patients treated with flutamide-LHRH analogue therapy had died. There was no significant difference in survival between treatment groups. The hazard ratio for time to death (survival) was 0.87 (95% confidence interval 0.72 to 1.05).

There was no significant difference in time to objective tumor progression between treatment groups. Objective tumor progression was defined as the appearance of any bone metastases or the worsening of any existing bone metastases on bone scan attributable to metastatic disease, or an increase by 25% or more of any existing measurable extraskeletal metastases. The hazard ratio for time to progression of Bicalutamide plus LHRH analogue to that of flutamide plus LHRH analogue was 0.93 (95% confidence interval, 0.79 to 1.10).

Quality of life was assessed with self-administered patient questionnaires on pain, social functioning, emotional well-being, vitality, activity limitation, bed disability, overall health, physical capacity, general symptoms, and treatment related symptoms. Assessment of the Quality of Life questionnaires did not indicate consistent significant differences between the two treatment groups.

5.3 PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year oral carcinogenicity studies were conducted in both male and female rats and mice at doses of 5, 15 or 75 mg/kg/day of bicalutamide. A variety of tumor target organ effects were identified and were attributed to the antiandrogenicity of bicalutamide, namely, testicular benign interstitial (Leydig) cell tumors in male rats at all dose levels (the steady-state plasma

concentration with the 5 mg/kg/day dose is approximately 2/3 human therapeutic concentrations*) and uterine adenocarcinoma in female rats at 75 mg/kg/day (approximately 1 1/2 times the human therapeutic concentrations*). There is no evidence of Leydig cell hyperplasia in patients; uterine tumors are not relevant to the indicated patient population.

A small increase in the incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (approximately 4 times human therapeutic concentrations*) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg/day (approximately 2/3 human therapeutic concentrations*) and above were recorded. These neoplastic changes were progressions of non-neoplastic changes related to hepatic enzyme induction observed in animal toxicity studies. Enzyme induction has not been observed following bicalutamide administration in man. There were no tumorigenic effects suggestive of genotoxic carcinogenesis. A comprehensive battery of both *in vitro* and *in vivo* genotoxicity tests (yeast gene conversion, Ames, *E. coli*, CHO/HGPRT, human lymphocyte cytogenetic, mouse micronucleus, and rat bone marrow cytogenetic tests) has demonstrated that bicalutamide does not have genotoxic activity.

Administration of bicalutamide may lead to inhibition of spermatogenesis. The long-term effects of bicalutamide on male fertility have not been studied.

In male rats dosed at 250 mg/kg/day (approximately 2 times human therapeutic concentrations*), the precoital interval and time to successful mating were increased in the first pairing but no effects on fertility following successful mating were seen. These effects were reversed by 7 weeks after the end of an 11-week period of dosing.

No effects on female rats dosed at 10, 50 and 250 mg/kg/day (approximately 2/3, 1 and 2 times human therapeutic concentrations, respectively*) or their female offspring were observed. Administration of bicalutamide to pregnant females resulted in feminization of the male offspring leading to hypospadias at all dose levels. Affected male offspring were also impotent.

*Based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:
Lactose Monohydrate Ph.Eur.
Sodium Starch Glycolate Ph.Eur.
Colloidal Silicon Dioxide Ph.Eur.
Povidone K-30 Ph.Eur.
Magnesium Stearate Ph.Eur.
Opadry White In-House (Y-1-7000)
Purified Water Ph.Eur.

6.2 Incompatibilities
Not known

6.3 Shelf life
36 Months

6.4 Special precautions for storage
Do not store above 30^{o}C.

6.5 Nature and contents of container
Bicalutamide tablets (BYPRO) are available in a blister strip of 10 tablets or 14 tablets. Carton containing following of the pack sizes
2 strips of 10 tablets
3 strips of 10 tablets
2 strips of 14 tablets

7. NAMES AND ADDRESS OF MARKETING AUTHORIZATION HOLDERS

Fresenius Kabi Oncology Ltd.
Echelon Institutional Area,
Plot No.-11, Sec-32
Gurgaon - 122001, Haryana, India

8. MARKETING AUTHORISATION NUMBER (S):

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

10. DATE OF REVISION OF THE TEXT: 09/2011

11. VERSION NUMBER: EXP/00/2011

Bicalutamide Tablets 50 mg
Blisters of 10 and 14 Tablets

Section 1.3.2 Product Monograph

1.3.2 Product Monograph:

Product Monograph is attached in below pages.

C_S = concentration of USP Bicalutamide RS in the *Standard solution* (mg/mL)
C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Des-fluoro analog[a]	0.74	0.2
2-Fluoro isomer[b]	0.78	0.2
Bicalutamide	1.00	—
Bicalutamide related compound B	1.12	—
Des hydroxy analog[c]	1.19	0.2
Individual unspecified impurity	–	0.1

[a] (*RS*)-4′-Cyano-3-phenylsulfonyl-2-hydroxy-2-methyl-3′-(trifluoromethyl)-propionanilide.
[b] (*RS*)-4′-Cyano-3-(2-fluorophenylsulfonyl)-2-hydroxy-2-methyl-3′-(trifluoromethyl)-propionanilide.
[c] (*RS*)-4′-Cyano-3-(4-fluorophenylsulfonyl)-2-methyl-3′-(trifluoromethyl)propionanilide.

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NMT 0.2%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Bicalutamide RS
  USP Bicalutamide Related Compound B RS
  (*RS*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-(3-fluorophenylsulfonyl)-2-hydroxy-2-methylpropanamide.
  $C_{18}H_{14}F_4N_2O_4S$ 430.37

Bicalutamide Tablets

» Bicalutamide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of bicalutamide ($C_{18}H_{14}F_4N_2O_4S$).

Packaging and storage—Preserve in tight containers. Store at controlled room temperature.

Labeling—When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

USP Reference standards ⟨11⟩**—**
USP Bicalutamide RS
USP Bicalutamide Related Compound B RS
(*RS*)-*N*-(4-Cyano-3-(trifluoromethyl)phenyl)-3-(3-fluorophenylsulfonyl)-2-hydroxy-2-methylpropanamide.
$C_{18}H_{14}F_4N_2O_4S$ 430.37

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Dissolution ⟨711⟩**—**

TEST 1—

Medium: 1.0% w/v sodium lauryl sulfate in water; 1000 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Standard solution—Transfer about 10 mg, accurately weighed, of USP Bicalutamide RS to a 200-mL volumetric flask, dissolve in 2 mL of tetrahydrofuran, and dilute with *Medium* to volume.

Test solution—Pass the solution under test through a suitable 0.45-µm filter.

Procedure—Determine the amount of $C_{18}H_{14}F_4N_2O_4S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 270 nm on portions of the *Test solution* in comparison with the *Standard solution,* using the *Medium* as the blank. Calculate the percentage of bicalutamide ($C_{18}H_{14}F_4N_2O_4S$) dissolved by the formula:

$$\frac{A_U \times C_S \times 1000 \times 100}{A_S \times L}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of bicalutamide in the *Standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—Not less than 80% (*Q*) of the labeled amount of bicalutamide is dissolved in 45 minutes.

TEST 2—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium, Apparatus 2, Time, Standard solution, Test solution, and *Procedure*—Proceed as directed for *Test 1*.

Tolerances—Not less than 75% (*Q*) of the labeled amount of bicalutamide is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

1% Sodium lauryl sulfate solution—Dissolve 15 g of sodium lauryl sulfate in 1.5 L of water.

Standard solution—Dissolve an accurately weighed quantity of USP Bicalutamide RS in a minimum amount of tetrahydrofuran, and dilute quantitatively with *1% Sodium lauryl sulfate solution* to obtain a solution having a known concentration of about 0.05 mg per mL.

Test solution—Transfer 1 Tablet to a 100-mL volumetric flask, add about 10 mL of water, and sonicate for approximately 30 minutes. Add about 80 mL of tetrahydrofuran, and sonicate for 30 minutes to complete dissolution of the bicalutamide. Allow to cool to room temperature, and dilute with tetrahydrofuran to volume. Pass this solution through a 0.45-µm suitable filter unit, transfer 10.0 mL of filtrate to a 100-mL volumetric flask, and dilute with *1% Sodium lauryl sulfate solution* to volume.

Procedure—Concomitantly determine the UV absorbances of the *Standard solution* and the *Test solution* with a suitable spectrophotometer at 270 nm, using *1% Sodium lauryl sulfate solution* as the blank. Calculate the quantity, in mg, of bicalutamide ($C_{18}H_{14}F_4N_2O_4S$) in the Tablet taken by the formula:

$$1000C(A_U / A_S)$$

in which C is the concentration, in mg per mL, of USP Bicalutamide RS in the *Standard solution;* and A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively.

Limit of 4-amino-2-(trifluoromethyl)benzonitrile—

Mobile phase and *System suitability solution*—Proceed as directed in the *Assay*.

Standard solution—Dissolve an accurately weighed quantity of USP Bicalutamide RS in tetrahydrofuran to obtain a solution having a known concentration of about 0.2 mg per mL. Transfer 5.0 mL of this solution to a 50–mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—Transfer an accurately weighed quantity of the powdered Tablet prepared in the *Assay preparation,* equivalent to about 50 mg of bicalutamide, to a 25-mL volumetric flask. Add about 2 mL of tetrahydrofuran, and allow to stand for 5 minutes. Add about 20 mL of *Mobile phase,* and sonicate for 10 minutes. Allow to cool to room temperature, and dilute with

Mobile phase to volume. Pass the sample through a suitable 0.2-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to use a liquid chromatograph equipped with a 220-nm detector.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of 4-amino-2-(trifluoromethyl)benzonitrile in the portion of Tablets taken by the formula:

$$100(1/1.4)(C_S / C_U)(r_U / r_S)$$

in which 1.4 is the relative response factor for 4-amino-2-(trifluoromethyl)benzonitrile, C_S is the concentration, in mg per mL, of USP Bicalutamide RS in the *Standard solution;* C_U is the concentration, in mg per mL, of bicalutamide in the *Test solution* based on the label claim; r_U is the peak area for 4-amino-2-(trifluoromethyl)benzonitrile obtained from the *Test solution;* and r_S is the peak area for bicalutamide obtained from the *Standard solution:* not more than 0.1% of 4-amino-2-(trifluoromethyl)benzonitrile is found. [NOTE—The relative retention time for 4-amino-2-(trifluoromethyl)benzonitrile is about 0.4.]

Assay—

Mobile phase—Prepare a mixture of water, tetrahydrofuran, and acetonitrile (65 : 20 : 15).

Standard preparation—Dissolve an accurately weighed quantity of USP Bicalutamide RS in tetrahydrofuran to obtain a solution having a known concentration of about 0.8 mg per mL. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Assay preparation—Grind not fewer than 20 Tablets to a fine powder. Transfer an accurately weighed quantity of powdered Tablets, equivalent to about 50 mg of bicalutamide, to a 100-mL volumetric flask. Add about 50 mL of tetrahydrofuran, and sonicate for at least 10 minutes to complete dissolution. Allow to cool to room temperature, and dilute with tetrahydrofuran to volume. Pass this solution through a suitable 0.45-µm filter. Transfer 4.0 mL of the filtrate to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

System suitability solution—Dissolve suitable quantities of USP Bicalutamide RS and USP Bicalutamide Related Compound B RS in tetrahydrofuran to obtain a solution having known concentrations of about 0.8 mg of USP Bicalutamide RS per mL and 0.4 mg of USP Bicalutamide Related Compound B RS per mL. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 270-nm detector, and a 5-mm × 12.5-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 50°. Chromatograph the *System suitability solution,* and record the peak areas as directed for *Procedure:* the relative retention time for the bicalutamide related compound B peak is about 1.1; the resolution, *R,* between bicalutamide and bicalutamide related compound B is greater than 1.9; the tailing factor of the bicalutamide peak is less than 1.3; and the relative standard deviation for replicate injections calculated for the bicalutamide peak is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the bicalutamide peaks. Calculate the quantity, in percentage of the label claim, of bicalutamide $C_{18}H_{14}F_4N_2O_4S$) in the portion of Tablets taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Bicalutamide RS in the *Standard preparation;* C_U is the concentration, in mg per mL, of bicalutamide in the *Assay preparation* based on the label claim; and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Biological Indicator for Dry-Heat Sterilization, Paper Carrier

» Biological Indicator for Dry-Heat Sterilization, Paper Carrier, is a defined preparation of viable spores made from a culture derived from a specified strain of *Bacillus subtilis* subspecies *niger*, on a suitable grade of paper carrier, individually packaged in a container readily penetrable by dry heat, and characterized for predictable resistance to dry-heat sterilization. The packaged Biological Indicator for Dry-Heat Sterilization, Paper Carrier, has a particular labeled spore count per carrier of not less than 10^4 and not more than 10^9 spores. When labeled for and subjected to dry-heat sterilization conditions at a particular temperature, it has a survival time and kill time appropriate to the labeled spore count and to the decimal reduction value (*D value*, in minutes) of the preparation, specified by:

Survival time (in minutes) = not less than (labeled *D value*) × (log labeled spore count per carrier − 2); and

Kill time (in minutes) = not more than (labeled *D value)* × (log labeled spore count per carrier + 4).

Packaging and storage—Preserve in the original package under the conditions recommended on the label, and protect from light, toxic substances, excessive heat, and moisture. The packaging and container materials do not adversely affect the performance of the article used as directed in the labeling.

Expiration date—The expiration date is determined on the basis of stability studies and is not less than 18 months from the date of manufacture, the date of manufacture being the date on which the first determination of the total viable spore count was made.

Labeling—Label it to state that it is a Biological Indicator for Dry-Heat Sterilization, Paper Carrier; to indicate its *D value* and the method used to determine such *D value*, i.e., by spore count or fraction negative procedure after graded exposures to the sterilization conditions; the survival time and kill time under the specified sterilization conditions stated on the label; its particular total viable spore count, with a statement that such count has been determined after preliminary heat treatment; and its recommended storage conditions. State in the labeling the size of the paper carrier, the strain and ATCC number from which the spores were derived, and instructions for spore recovery and for safe disposal of the indicator. Indicate in the labeling that the stated *D value* is reproducible only under the exact conditions under which it was determined, that the user would not necessarily obtain the same result, and that the user should determine the suitability of the biological indicator for the particular use.

Identification—The biological indicator organism complies substantially with the morphological, cultural, and biochemical characteristics of the strain of *Bacillus subtilis*, ATCC No. 9372, designated subspecies *niger*, detailed for that biological indicator organism under *Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier*.

Resistance performance tests—

D value—Proceed as directed for the relevant procedure for *D Value* under *Biological Indicators—Resistance Performance*